

@Title: Model for Deltamethrin kinetics
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@BEGIN Description
Model for pyrethroid absorption, distribution, and metabolism. The parameter values in the current file are for deltamethrin, with physiological parameters for rats, but the intent is for the model structure to be the same for any pyrethroid, and humans as well as rats.

@END Description
@BEGIN DOC
This is a translation of Matlab code by Mirfazaelian et al., modified by Rogelio Tornero and Steve Godin. The translation closely follows the original code; the ODEs are largely in the same order as in the original. State variables are slightly reordered.
@END Doc

BEGIN VARIABLES

BEGIN STATE # Names and initial values, or comma-separate list in KEEP
Defined via differential equations.
Fecal elimination
FEC = 0.0 @ (umol) Amt eliminated in feces;

Dosing - Oral route
ASTM = stomach @ (umol) Amt in stomach;
AINT = 0.0 @ (umol) Amt in intestines;
Oral = 0.0 @ (umol) Amt absorbed via the oral route;

Metabolic pathways
CaEP = 0.0 @ (umol) Amt hydrolized in plasma;
CYP = 0.0 @ (umol) Amt oxidized in liver;
CaE = 0.0 @ (umol) Amt hydrolized in liver;

ABL = 0.0 @ (umol) Amt in blood;
AEF = 0.0;
AIF = 0.0;
AER = 0.0;
AIR = 0.0;
AES = 0.0;
AIS = 0.0;
AEBRN = 0.0;
AIBRN = 0.0;
AEL = 0.0;
AIL = 0.0;
AHYD = 0.0;
EXCR = 0.0 @ (umol) Amt excreted in urine;

Dosing - IV route
rIV = initrIV @ (umol/hr) rate of injection;

END # State

Derived variables

UER @ Rate of urinary elimination;
CA @ Concentration in arterial blood;

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CVF;
CIF;
CVS;
CIS;
CVR;
CIR;
CVBRN;
CVL;
CIL;
CV;
END #VARIABLES
# ++++++
BEGIN PARAMETERS
# Dose-related -----
# Oral gavage:
oraldose = 0.0      @ (mg/kg) oral gavage dose;
stomach = oraldose * BW * mol @ (umol) initial amount in the stomach;

# IV Injection:
ivdose=0.0          @ (mg/kg) IV dose;
Tinf=0.005           @ (h) duration of infusion;
initrIV = ivdose*BW*mod/Tinf @ (umol/hr) initial rate of injection;
# Physiological Parameters (These are rat values) -----
BW    = 0.41          @ kg;
QCC   = 14.10          @ (L/h) for a 1 kg animal. Scales as BW^0.75. Brown et al [60 * 0.235];
QC    = QCC*BW^0.75

QLC   = 18.3/100       @ fractional cardiac output to liver;
QFC   = 7/100           @ fractional cardiac output to fat;
QBRNC = 2/100           @ fractional cardiac output to brain;
QSC   = 23.6/100        @ fractional cardiac output to slowly;
QRC   = 1-QLC-QFC-QBRNC-QSC @ fractional cardiac output to richly;

QL    = QC*QLC         @ (L/h) cardiac output to liver;
QF    = QC*QFC         @ (L/h) cardiac output to fat;
QBRN  = QC*QBRNC       @ (L/h) cardiac output to brain;
QS    = QC*QSC         @ (L/h) cardiac output to slowly;
QR    = QC*QRC         @ (L/h) cardiac output to richly;

VBLC  = 7.00/100        @ fractional blood volume;
VLC   = 3.00/100        @ fractional liver volume;
VFC   = 7.00/100        @ fractional fat volume;
VBRNC = 0.5/100         @ fractional brain volume;
VSC   = 78/100          @ fractional slowly volume;
VRC   = 1-VBLC-VLC-VFC-VBRNC-VSC @ fractional richly volume;

VBL   = BW * VBLC       @ (L) blood volume;
VL    = BW * VLC         @ (L) liver volume;
VF    = BW * VFC         @ (L) fat volume;
VBRN  = BW * VBRNC       @ (L) brain volume;
VS    = BW * VSC         @ (L) slowly volume;
VR    = BW * VRC         @ (L) richly volume;

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# Blood Volume Fraction Brown et al p.458
BVF = 0.025;
BVS = 0.04;
BVRN = 0.03;
BVL = 0.21;
BVR = 0.21;

/* balance calculations, independent of model
   each should be 100
*/

volbal = 100 -(BW-(VBL+VL+VF+VBRN+VS+VR));
flowbal = 100 -(QC-(QL+QF+QBRN+QS+QR));

# Deltamethrin specific parameters -----
MW = 505.          @ (ug/umol) Molecular weight;
mol= 1000/MW        @ (umol/mg) correction factor for mg-->umol;

# Distribution ratios
PBRN = 0.14         @ brain/plasma (Measured);
PL = 19              @ liver/plasma;
PR = 8.10            @ rapid/plasma (Set to DRL);
PS = 5.64            @ slowly/plasma (Measured);
PF = 75              @ fat/plasma ;

# Diffusion-Limited
# Tissue Permeability Area-cross Product (L/hr)
# Fitted
PALC = 0.28          @ (L/hr) Liver;
PAFC = 0.025          @ (L/hr) Fat;
PABRNC = 0.002        @ (L/hr) Brain;
PASC = 0.043          @ (L/hr) Slowly;
PARC = 0.093          @ (L/hr) Rapidly;

PAL= PALC*QL;
PAF= PAFC*QF;
PABRN= PABRNC*QBRN;
PAS= PASC*QS;
PAR= PARC*QR;

# Liver metabolic clearance
CLOX = 5.3            @ (L/h/kg);
CLEST = 0.0             @ (L/h/kg);
KBLD = 0.0012          @ (L/h/ml) serum;

#Uptake rate constants (/hr)
KSI = 0.42             @ (/hr) compartment transfer rate;
KS = 0.0                @ (/hr) stomach uptake rate;
KI = 1.51               @ (/hr) intestinal uptake rate;
KFEC = 0.59              @ (/hr) fecal excretion;

# Urinary excretion
KEL = 0.0586            @ (/hr);
VDISTC = 1               @ (L/h/kg);

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END # Parameters

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BEGIN CONTINUOUS

Define concentrations based on state variable (amounts)

I intracellular

E extracellular

CA = ABL/VBL;

CVF = AEF/(VF*BVF);

CIF = AIF/(VF*(1-BVF));

CVS = AES/(VS*BVS);

CIS = AIS/(VS*(1-BVS));

CVR = AER/(VR*BVR);

CIR = AIR/(VR*(1-BVR));

CVBRN = AEBRN/(VBRN*BVBRN);

CIBRN = AIBRN/(VBRN*(1-BVBRN));

CVL =

AEL/(VL*BVL);

CIL = AIL/(VL*(1-BVL));

Concentration in the blood compartment and blood clearance

CV = (QF*CVF + QR*CVR + QS*CVS + QBRN*CVBRN + QL*CVL)/QC;

CaEP' =

Kbld*VBL*CA; # blood clearance via esterases (umol/h)

ABL' = QC*CV - QC*CA - CaEP' + rIV;

Oral uptake and fecal excretion

FEC' = Kfec*AINT; # fecal clearance (umol/hr)

ASTM' = -Ks*ASTM - Ks*ASTM; # rate of change in stomach

AINT' = Ks*ASTM - Ki*AINT - FEC'; # rate of change in intestine

Oral' = Ks*ASTM + Ki*AINT; # rate via oral pathway

AHYDabolism

CYP' = CLox*CIL;

CaE' = CLest*CIL;

diffusion-limited compartments

AEF' = QF*(CA-CVF) + PAF*(CIF/PF-CVF); # (umol/hr)

AIF' = PAF*(CVF-CIF/PF);

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AER' = QR*(CA-CVR) + PAR*(CIR/PR-CVR);    # (umol/hr)
AIR' = PAR*(CVR-CIR/PR);

AES' = QS*(CA-CVS) + PAS*(CIS/PS-CVS);    # (umol/hr)
AIS' = PAS*(CVS-CIS/PS);

AEBRN' = QBRN*(CA-CVBRN) + PABRN*(CIBRN/PBRN-CVBRN); # (umol/hr)
AIBRN' = PABRN*(CVBRN-CIBRN/PBRN);

AEL' = QL*(CA-CVL) + PAL*(CIL/PL-CVL) + Oral';    # (umol/hr)
AIL' = PAL*(CVL-CIL/PL) - CYP' - CaE';

***** classical compartment approach for urinary AHYDabolites
urinary AHYDabolites arise by hydrolysis
rAHYD= production to body compartment - loss from body compartment
via urinary elimination
rEXCR = rate of excretion of urinary metabolites
*****
AHYD' = CaE' - KEL*AHYD; #(umol/hr)
EXCR' = KEL*AHYD;    #(umol/hr)

# retain rate of excretion of AHYDabolites (umol/hr)
UER = rEXCR;

END # Continuous

# ++++++
BEGIN JUMPS
EVENT stop-infusion {
    rIV = 0.0;
}
TRIGGER when_stop-infusion {
    Time == Tinf;
}
ACTIONS {
    when_stop-infusion stop-infusion;
}
END # Jumps

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